Antibiotic developed 50 years ago may be the key to fighting 'superbugs'

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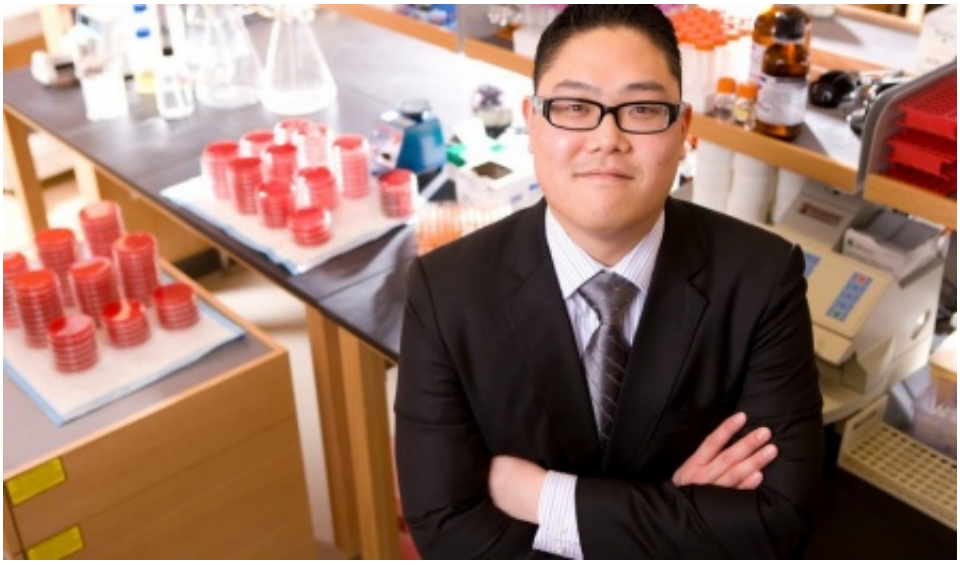

Brian Tsuji will lead an international research team on the largest NIH grant in the history of the UB School of Pharmacy and Pharmaceutical Sciences, and the largest active R01 at UB and among departments of clinical pharmacy in the U.S.

(Medical Xpress)—Scientists at the University at Buffalo are turning to an old class of antibiotics to fight new superbugs resistant to modern medicine.

A $4.4 million grant from the National Institutes of Health will allow UB researchers to develop new dosing regimens for polymyxin antibiotics.

Developed more than 50 years ago, polymyxins were not subject to modern antibiotic drug development standards. And they have proved to be toxic to both the kidneys and nervous system.

But they're also effective against superbugs such as Acinetobacter baumannii, Pseudomonas aeruginosa, Klebsiella pneumoniae and other gram-negative bacteria that are resistant to all current antibiotics and which can cause a variety of diseases, ranging from pneumonia and other respiratory infections, to serious blood or wound infections.

The grant is the largest NIH grant in the history of the UB School of Pharmacy and Pharmaceutical Sciences, and the largest active R01 at UB and among departments of clinical pharmacy in the U.S. The research is led by Brian Tsuji, PharmD, associate professor and director of clinical research in the Department of Pharmacy Practice.

The aim of the project is to evaluate novel dosing regimens for polymyxin combinations to maximize antibacterial activity and to minimize the emergence of resistance and toxicity, says Tsuji, principal investigator on the grant.

Tsuji and his team will then translate this knowledge back to the bedside by proposing new, optimal regimens that can be utilized by patients.

Gram-negative bacteria, which do not retain a gram-staining process used in the laboratory to differentiate bacteria, are causing a global health crisis, Tsuji explains.

"This is a massive public health problem because the emergence of these new highly resistant strains has been coupled with a dwindling pipeline of development and approval for new drugs," he says.

Polymyxins remain a viable option, but there is mounting evidence that

resistance even to polymyxins is also increasing, Tsuji notes, and no new antibiotics will be available for these superbugs for many years to come.

Because of this, clinicians often are left with little or no option but to use polymyxins (polymyxin B and colistin, i.e. polymyxin E). Resistance to polymyxins is increasing because plasma concentrations at recommended daily doses are not effective in reducing infection in critically ill patients. Increasing the dose is not an option because they may cause kidney toxicity at higher doses.

"Therefore," Tsuji says, "we needed to think innovatively and differently about how to attack this problem."

Researchers will use an innovative Hollow Fiber Model System in Tsuji's lab to mimic the concentrations of antibiotics in patients against bacteria from critically ill patients.

"We want to mimic conditions seen in real patients who are infected with these deadly strains by using model systems that mirror exact drug concentrations in the body," he says. "In the lab, we can study these combination regimens very intensely over the same time frame that we would treat a patient with bacterial pneumonia (14 days) to understand the fundamental basis for drug resistance.

"This will allow us to address the public health disaster of antimicrobial resistance and to fight these deadly infections in severely ill patients where no traditional treatments exist."

Tsuji has put together a team of world-renowned experts in polymyxin pharmacology, genomics, animal models and pharmacokinetics/pharmacodynamics (PK/PD).

The international, interdisciplinary team is also co-led by Jian Li, PhD,

PI, and includes Roger Nation, PhD, and John Boyce, PhD, all from Monash University, Melbourne, Australia; and Thomas Walsh, MD, and Vidmantas Petraitis, MD, from Weill Cornell Medical College, New York City.

The research team also includes experts in PK/PD, including Alan Forrest, PharmD, and Gauri Rao, PharmD, from the UB Department of Pharmacy Practice, and former UB postdocs Juergen Bulitta, PhD, and Cornelia Landersdorfer, PhD, both now of Monash University.

The team of Forrest, Bulitta, Landersdorfer and Rao, which will develop mathematical models to perform computer simulations that propose optimal doses of polymyxin combinations for patients in the study, was critical for the success of the grant, Tsuji says.

Technicians and students in his lab, including Patricia Holden and Neang Ly, generated key preliminary data to make the grant possible.

Provided by University at Buffalo